Med. čas. 2026; 60(1): 31-41.
REVIEW ARTICLE
doi: 10.5937/mckg60-60288
COBISS . SR - ID 194792457
UDK. 616.94-074

FIBRINOLYSIS DISORDERS IN SEPSIS: THE IMPORTANCE OF EARLY DETECTION OF ABNORMALITIES IN SEPSIS-INDUCED COAGULOPATHY AND AVAILABLE LABORATORY MARKERS OF FIBRINOLYSIS

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ПОРЕМЕЋАЈИ ФИБРИНОЛИЗЕ У СЕПСИ: ЗНАЧАЈ РАНОГ ОТКРИВАЊА АБНОРМАЛНОСТИ У СЕПСОМ ИЗАЗВАНОЈ КОАГУЛОПАТИЈИ И ДОСТУПНИ ЛАБОРАТОРИЈСКИ МАРКЕРИ ФИБРИНОЛИЗЕ

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ABSTRACT

Sepsis is a life-threatening organ dysfunction caused by an ineffective host response to infection. Some of the most prevalent disorders in sepsis are hemostatic disorders. Sepsis often develops a state of impaired anticoagulant activity and fibrinolysis suppression, called sepsis-induced coagulopathy. Damage to the fibrinolytic system has increasingly been considered a key factor in sepsis-induced coagulopathy. Impaired fibrinolysis in sepsis can contribute to undesirable outcomes such as microvascular thrombosis, organ dysfunction, and increased mortality. Given that one of the postulates related to sepsis is that prompt diagnosis and quick care are necessary, it would be of great importance to diagnose various forms of coagulopathies in sepsis at the beginning of their occurrence, for an adequate therapeutic approach. In this sense, easily accessible, routine diagnostic tests are necessary. Conventional laboratory tests for coagulopathies so far fail to fully define sepsis-induced coagulopathy. Particularly challenging is the testing of hypofibrinolysis in routine practice. The objectives of our study were to review the available scientific literature to investigate the relationship between inflammation and coagulation in sepsis, fibrinolysis disorders in sepsis-induced coagulopathy, to determine the importance of early recognition of these disorders in sepsis, and to investigate the available laboratory markers of fibrinolysis and coagulopathies.

Key words: *sepsis; blood coagulation disorders; fibrinolysis; blood viscosity; hematologic tests.*

САЖЕТАК

Сепса представља животно угрожавајућу дисфункцију органа узроковану неефикасним одговором домаћина на инфекцију. Неки од најзаступљенијих поремећаја у сепси јесу хемостазни поремећаји. Код сепсе се често развија стање поремећене антикоагулантне активности и супресије фибринолизе, које се назива сепсом изазвана коагулопатија. Оштећење фибринолитичког система све више се сматра кључним фактором у коагулопатији изазваној сепсом. Оштећена фибринолиза у сепси може допринети нежељеним исходима као што су микроваскуларна тромбоза, дисфункција органа и повећан морталитет. С обзиром на то да је један од постулата везан за сепсу, да су неопходни брза дијагностика и брзо збрињавање, било би веома значајно да се различити облици коагулопатија у сепси дијагностикују чим настану ради адекватног терапијског приступа. У том смислу, неопходни су лако доступни, рутински дијагностички тестови. Досадашњи конвенционални лабораторијски тестови коагулопатија не успевају да у потпуности дефинишу сепсом изазвану коагулопатију. Посебно је изазовно тестирање хипофибринолизе у рутинској пракси. Циљеви нашег истраживања били су да прегледом доступне научне литературе истражимо везу између запаљења и коагулације у сепси, поремећаје фибринолизе у сепсом изазваној коагулопатији, утврдимо значај раног препознавања ових поремећаја у сепси и доступне лабораторијске маркере фибринолизе и коагулопатија.

Кључне речи: *сепса; поремећаји коагулације крви; фибринолиза; вискозност крви; хематолошки тестови.*

INTRODUCTION

The traditional definition of sepsis is "a systemic inflammatory response syndrome caused by infection" (1). Definitions of sepsis have evolved over the years, as the pathobiology of sepsis is not yet fully understood (2). In 2016, this definition was updated by the Third International Consensus Definition for sepsis to "life-threatening organ dysfunction caused by an ineffective host response to infection," shifting the focus from inflammation to organic dysfunction (1).

The epidemiological and clinical significance of sepsis is extremely high. 19 million cases of sepsis are diagnosed annually, with almost 5 million deaths, making it the leading cause of mortality in the world (1). A group of

Primljen/Received: 20.07.2025.
Prihvaćen/Accepted: 03.10.2025.

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doi: 10.5937/mckg60-60288
COBISS . SR - ID 194792457
UDK. 616.94-074

authors for 2017 made an estimate of 48.9 million cases and 11 million deaths associated with sepsis worldwide, which represents 20 % of all global deaths (3). The severity of sepsis is often described in relation to organic dysfunction, and for the purpose of assessing this dysfunction, we are provided with the following scores: Sequential Organ Failure Assessment and Quick Sequential Organ Failure Assessment (4).

The criteria for the assessment of sequential organ failure are given in Table 1 (5). Organ dysfunction is defined as an acute change in the overall score of sequential organ failure by two or more points caused by infection (4, 5).

Also, it is of utmost importance to monitor patients with infection who are likely to develop sepsis outside the intensive care unit, and in this sense, a quick Sequential Organ Failure Assessment score is available, for clinicians to quickly and repeatedly use for patient evaluation. Criteria for determining the quick score of sequential organ failure are given in Table 2 (6). This score does not define sepsis, but it allows for the rapid identification of patients at potential risk of developing sepsis. In this sense, the presence of at least two criteria suggests that the patient is at high risk of adverse outcomes, such as death in hospital or prolonged intensive care management (4).

The Third International Consensus Definition for sepsis, abolished the stage of "severe sepsis", and now includes only sepsis and septic shock. The reason for this is that early detection of sepsis, with timely and appropriate interventions, increases the likelihood of survival of patients with sepsis (7). On the other hand, shock is defined as a subgroup of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone, with severe hypotension, increased lactate levels, the need for vasopressor therapy, and adequate fluid restitution (6), respectively, as the need for norepinephrine treatment to maintain mean arterial pressure > 65 mm Hg (8).

MATERIAL AND METHODS

The objectives of our paper were to search the relevant literature to investigate: a) interaction between inflammation and coagulation in sepsis, b) fibrinolysis disorders in sepsis-induced coagulopathy through different stages of organic dysfunction of patients with sepsis, c) importance of early recognition of these disorders in sepsis, d) laboratory markers of fibrinolysis and coagulopathy available in clinical practice. The search for relevant available scientific literature was carried out on the basis of databases of scientific research papers: PubMed, KoBSON, Science Direct, Google Scolar, SpringerOpen. Papers published from 2001 to the present are analyzed. Key words for the search were: definitions of sepsis, sequential organ failure score, sepsis-induced coagulopathy, resistance to fibrinolysis, viscoelastic tests, plasma factors of fibrinolysis, time of euglobulin lysis.

RESULTS

The relationship between inflammation and coagulation in sepsis

Infection, and sepsis in particular, cause multiple and complex disorders in many systems, including the coagulation cascade. The vast majority of patients with sepsis present with hemostatic abnormalities, ranging from subclinical coagulopathy to fulminant disseminated intravascular coagulation. During the initial stages of infection, coagulation acts as a natural defense mechanism, trying to limit the responsible pathogen and prevent its spread into the systemic circulation. However, in sepsis, the massive production of inflammatory cytokines and their release into the circulation leads to excessive activation of the coagulation process, impaired fibrinolysis and suppression of anticoagulant mechanisms. The hemostatic balance is significantly disturbed in sepsis is a coagulation process, while anticoagulant mechanisms, including fibrinolysis and anticoagulant factors, are suppressed. Patients with sepsis are prone to a prothrombotic state through four main mechanisms: activation of the external coagulation pathway, cytokine-induced enhancement of coagulation, suppression of anticoagulant pathways, and fibrinolysis impairment (1).

The main trigger for coagulation activation in sepsis is the release of tissue factor. Tissue factor is located in the vascular endothelium, and its exposure to circulation in case of endothelial damage leads to activation of the external coagulation pathway. However, this is not the primary mechanism of tissue factor activation in sepsis. Tissue factor is also present in inflammatory cells, mainly monocytes and other circulating macrophages (1). In septic patients, pathogens release a large number of pathogen-associated molecular patterns (e.g., lipopolysaccharide), which are recognized by pattern recognition receptors on the cell surface of several immune cells (e.g., monocytes). Activated monocytes and macrophages release a variety of inflammatory mediators, cytokines and chemokines, which in turn activate neutrophils, platelets, and endothelial cells. Also, activated monocytes release extracellular vesicles that express procoagulant tissue factor on their surfaces. Therefore, tissue factor is released into the circulation and the external coagulation pathway is activated. Neutrophils also play a significant role in activating the coagulation cascade through tissue factor expression. Tissue factor-mediated thrombin formation, as well as the resulting fibrin formation in sepsis, leads to prothrombotic

doi: 10.5937/mckg60-60288
COBISS . SR - ID 194792457
UDK. 616.94-074

Table 1. Sequential organ failure assessment score.

Criteria	1	2	3	4
Respiration PaO2/FiO2 (mm Hg)	<400	<300	<200 (With respiratory support)	<100 (With respiratory support)
Coagulation 10^{-3}/ platelets/mm	<150	<100	<50	<20
Bilirubin mg/dL	1.2–1.9	2–5.9	6–11.9	>12
Bilirubin (μM)	(20-32)	(33-101)	(102-204)	(>204)
Cardiovascular hypotension	MAP < 70 mm Hg	Dopamine ≤ 5 or dobutamine (any dose)	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
CNS Glasgow Coma Score	13–14	10–12	6–9	<6
Creatinine, mg/dL	1.2–1.9	2–3.4	3.5–4.9	>5
Creatinine, (μM)	(110-170)	(171-299)	(300–440)	(>440)
Diuresis			or <500 mL/d	or <200 mL/d

Table 2. Quick score of assessment of sequential organ failure.

Criteria	0	1
Mental status	Not modified	It has been modified
Systolic blood pressure	>100 mmHg	≤ 100 mmHg
Respiratory rate	< 22/min	≥ 22/min

Table 3. Score of sepsis-induced coagulopathy.

Criteria	Value	Score (points)
Platelet count (x 10^9/L)	<100	2
	≥100<150	1
INR	>1.4	2
	>1.2 - ≤ 1.4	1
Sequential organ failure score	≥2	2
	1	1

≥ 4 is manifested by sepsis-induced coagulopathy

coagulation disorders through the formation of disseminated intravascular fibrin deposits (1, 9).

Recent studies have shown that inflammation and coagulation together contribute to the pathogenesis of organ dysfunction (10). Activated leukocytes, platelets, and endothelial damage are also known to play a key role in thromboinflammation in sepsis (11). As a consequence, microthrombi that form in the capillaries lead to poor circulation in the tissues and subsequent organ dysfunction in sepsis (12).

In sepsis, the manifestation of a two-way interaction between inflammation and coagulation is very significant, resulting in a self-sustaining cycle. Systemic activation of the innate immune system leads to a severe and persistent inflammatory response characterized by excessive release of inflammatory cytokines such as interleukin 1, interleukin-6 and tumor necrosis factor α, a condition designated as "cytokine storm" (13), which induces a coagulation cascade. Recently, it has been discovered that compensatory anti-inflammatory pathways are activated shortly after the onset of sepsis. The characteristic cytokine is intereleukin - 10, which is produced by various leukocytes, and which suppresses the production of interleukin - 6 (13). At the same time, various disrupted hemostatic mechanisms further maintain and enhance the inflammatory process. Among the coagulation factors, thrombin is a key mediator linking inflammation and coagulation, which involves additional activation of monocytes, neutrophils, platelets, and endothelial cells by binding to the thrombin receptor (11). In the early stages of sepsis, coagulation activation is prevented by three anticoagulant pathways: antithrombin III, protein C, and tissue factor inhibitor. Significant cross-interaction also exists between anticoagulant factors and inflammatory mediators. Antithrombin binds directly to inflammatory cells and suppresses the expression of cytokine receptors. In addition, activated protein C has been shown to reduce endotoxin-induced production of tumor necrosis factors-α, interleukin-1β, interleukin-6, and interleukin-8 by monocytes and macrophages. Inhibition of leukocyte activation may be another role of activated protein C. As sepsis progresses, the three anticoagulant mechanisms are disrupted, resulting in a hypercoagulant state. Antithrombin, an important anticoagulant mechanism that inhibits thrombin and factor Xa, is reduced in sepsis due to reduced synthesis and increased degradation via proteases and neutrophilic elastases. Normal activation of protein C is mediated by the thrombin-thrombomodulin complex on endothelial cells, leading to inhibition of factors Va and VIIIa. In addition, the endothelial protein C receptor is expressed on the surface of endothelial cells and further enhances the activation of protein C. However, protein C

doi: 10.5937/mckg60-60288
COBISS . SR - ID 194792457
UDK. 616.94-074

Table 4. Disseminated intravascular coagulation score.

Criteria	Value	Score (points)
An international normalized relationship (reference range <1.2)	<1.3	0
	1.3 - 1.6	1
	>1.6	2
Fibrin D-dimer (mg/L) (reference range: age-specific)	<0.8	0
	≥ 0 .8 – 8.0	2
	>8.0	3
Platelet count (x 10^9/L) (reference range 145-400)	>100	0
	>50-100	1
	<50	2
Fibrinogen (μmol/L) (reference range: 5.5-12)	≥2.94 (equivalent ≥ 1 g/L)	0
	<2.94 (equivalent < 1 g/L)	1

≥ 5 disseminated intravascular coagulation is manifested

Table 5. Rotational thrombolastometry tests.

Test	The mechanism of activation of clot formation	Factors that are evaluated by the test
Extem	Thromboplastin (tissue factor)	VII, X, V, II, I, platelets, fibrinolysis
Intem	Ellagic acid	XII, XI, IX, VIII, X, V, II, I, platelets, fibrinolysis
Fibtem	Thromboplastin (tissue factor) with the addition of cytochalazine D (platelet inhibitor)	Fibrinogen levels and fibrin polymerization
Aptem	Thromboplastin (tissue factor) with the addition of aprotinin or tranexamic acid, an inhibitor of fibrinolysis	Comparison of aptem with extem. Pathological and fulminant (< 20 min. fibrinolysis). To evaluate the effect of antifibrinolytics.
Ecarin	Contains ecarin, does not contain calcium chloride, which is why it is not sensitive to the effects of FXIII and TAFI	The earliest detection of fibrinolysis. To monitor direct thrombin inhibitors.
Tissue plasminogen activator	Tissue plasminogen activator	To detect the manifestation of resistance to fibrinolysis, i.e. "quenching" fibrinolysis. To evaluate the effects of antifibrinolytics.

Table 6. Rotational Thrombelastometry Test Parameters.

CT	Time from the beginning of the measurement to the initiation of coagulation (s)
CFT	Time from the beginning of clotting to the formation of a clot of 20 mm (s)
A5	Amplitude 5 minutes after CT scan (mm)
MCF	Maximum clot strength (mm)
CLI(x)	Clot lysis index x min after CT/ (% MCF)
ML	Maximum lysis (%)
LT	The Time of the League (s)
α	Alpha angle (°)

levels are lowered in sepsis. Finally, the tissue factor inhibitor inactivates the tissue factor-factor VIIa complex and is produced by several cells, including endothelial cells, but its levels are reduced in sepsis, resulting in unregulated inactivation of the tissue factor-factor VIIa complex (1).

In addition, there is an interaction between hemostasis and complement, which plays an important role in disseminated intravascular coagulation. In addition to converting fibrinogen to fibrin, thrombin also interacts closely with the complement system. The complement system plays a vital role in the communication between the innate immune system, coagulation, fibrinolysis, and cellular interactions in various infectious diseases. The primary role of the complement system is to enhance the host's defensive responses against pathogen invasion. However, an activated complement system can cause damage to host cells. Among complement factors, C3 and C5 are particularly important in the development of thromboinflammation. Activated C3a and C5a increase

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COBISS . SR - ID 194792457
UDK. 616.94-074

the production of inflammatory mediators. Moreover, C5a transforms the leukocyte membrane into a procoagulant platform. C3a also recruits and activates immune cells, such as neutrophils, eosinophils, and macrophages. The binding of C3b to the complement receptor on the endothelium can trigger signaling pathways within endothelial cells, leading to their activation. Activated endothelial cells can release inflammatory mediators and express adhesion molecules, further promoting immune cell recruitment and an inflammatory response (9, 11, 13).

Some studies point to the effect of the tertiary stage of coagulation – fibrinolysis, on the immune response. Plasmin has been shown to have an immunosuppressive effect due to its ability to modulate cytokine expression (14). Suppression of fibrinolysis is somewhat beneficial as it initially serves as a defense mechanism by which bacterial pathogens are confined to the fibrin network at the site of infection. However, reducing the process of fibrinolysis also has negative consequences: it prevents the unhindered flow of oxygen to the tissues, which leads to hypoxia and damage to tissues and organs (1, 15).

Sepsis-induced coagulopathy

As we have already stated, some of the most common disorders in sepsis are hemostatic disorders. Physiological hemostasis is a balance between the pro- and anticoagulant pathways, and in sepsis, this balance is disturbed, resulting in systemic thrombin formation, impaired anticoagulant activity, and suppression of fibrinolysis, which together form a condition called sepsis-induced coagulopathy. Depending on the balance between the procoagulant, anticoagulant and fibrinolytic pathways, various manifestations of sepsis-induced coagulopathy may manifest themselves: excessive activation of coagulation, formation of microvascular thrombi, impaired organ perfusion, organ dysfunction and bleeding. For the purpose of detection and monitoring of this disorder, the International Society of Haemostasis and Thrombosis Sepsis-Induced Coagulopathy Score was defined with the following criteria: Sequential Organ Failure Score, Platelet Level, Prothrombin Time/International Normalized Ratio (16).

Within the hemostatic system, an important physiological system is the fibrinolytic system, also called the plasminogen-plasmin system, which plays a key role in hemostatic equilibrium at the tertiary hemostasis level. Fibrinolysis is the process of breakdown of fibrin by plasmin and is activated when fibrin is formed as the end product of blood coagulation. Thus, the fibrinolytic system is crucial in regulating intravascular deposition and clearance of fibrin, maintaining hemostasis, and avoiding thrombosis (17).

The conversion of the plasminogen proenzyme to the active enzyme plasmin is a central step in the fibrinolytic system. Plasmin breaks down fibrin into soluble fibrin breakdown products. Two physiological plasminogen activators are capable of catalyzing plasminogen conversion: tissue plasminogen activator and urokinase plasminogen activator. The most important plasminogen activator for fibrin degradation is probably the tissue plasminogen activator, although the urokinase activator may also be involved in the complementary action of tissue- and urokinase plasminogen activators. In the absence of fibrin, the tissue plasminogen activator is a weak plasminogen activator. However, in the presence of fibrin, its activity is twice as high as a result of the binding of the tissue activator plasminogen and plasminogen to fibrin and the formation of a cyclic complex. Inhibition of the fibrinolytic system can occur at the plasminogen level, mainly by plasminogen-1 activator inhibitor. Plasminogen-2 activator inhibitor effectively inhibits tissue plasminogen and urokinase plasminogen activator, but plasma levels of this inhibitor are normally low or even undetectable (except during pregnancy). Inhibition of the fibrinolytic system can also occur at the plasmin level, mainly α2-antiplasmin. The degradation of fibrin is further inhibited by a thrombin-activated fibrinolysis inhibitor. This inhibitor is the link between coagulation and fibrinolysis. The antifibrinolytic activity of thrombin-activated fibrinolysis inhibitor is based on the elimination of C-terminal lysine and arginine residues from partially degraded fibrin, resulting in a strongly reduced binding of plasminogen to partially degraded fibrin and a concomitant decrease in plasminogen activation (18, 19).

In sepsis, fibrinolytic activity depends on the balance between tissue plasminogen activator and plasminogen activator inhibitors (20). Tissue plasminogen activator facilitates fibrinolysis through the breakdown of fibrin by plasmin, while plasminogen activator inhibitor suppresses fibrinolysis. In the early transitional phase of sepsis, fibrinolysis is increased due to the conversion of plasminogen to plasmin by the enhanced action of the tissue activator plasminogen. Subsequently, with an increase in plasminogen activator inhibitors and thrombin-activated fibrinolysis inhibitors, fibrinolysis damage occurs, which contributes to a hypercoagulable state in sepsis (21).

Damage to the fibrinolytic system is considered a key factor in sepsis-induced coagulopathy. Impaired fibrinolysis in sepsis can contribute to undesirable outcomes such as microvascular thrombosis, organ dysfunction, and increased mortality (22). The mechanisms underlying fibrinolysis resistance include decreased expression and/or release of the tissue plasminogen activator, decreased effect of this activator and/or plasmin due to elevated inhibitor levels, increased

doi: 10.5937/mckg60-60288
COBISS . SR - ID 194792457
UDK. 616.94-074

consumption, and/or increased clearance (23). Early inhibition of plasminogen activation leads to acute cessation of fibrinolysis, which is associated with increased morbidity and mortality in patients with sepsis (9).

Given the resistance to fibrinolysis that is manifested in sepsis and leads to organ dysfunction, research into the disruption of the level of natural anticoagulants in sepsis is still important. Antithrombin is an anticoagulant that inactivates thrombin and clotting factors IXa, Xa, XIa and XIIa. Patients with antithrombin deficiency are at risk of arterial and venous thrombosis. Protein C contributes to the inactivation of factor VIII. Protein C deficiency may be associated with severe thrombotic events. Protein S acts as a major cofactor for protein C. Protein S deficiency increases the risk of venous thrombosis (24). Another natural anticoagulant is thrombomodulin. In sepsis, the expression of thrombomodulin in endothelial cells is strongly reduced, causing impaired activation of protein C. Also, thrombomodulin has pronounced immunomodulatory effects (25). The role of thrombomodulin and the effects of its replacement in sepsis-induced coagulopathy have been the subject of intensive study (26).

A common companion of septic conditions is disseminated intravascular coagulation, which can be considered the final stage of sepsis-induced coagulopathy (16). Disseminated intravascular coagulation in sepsis is characterized by the formation of thrombin as a result of injury to endothelial cells caused by infection. There is a widespread occurrence of microvascular blood clots and concomitant bleeding caused by the consumption of clotting factors and platelets. This severe coagulopathy can lead to multiple organ dysfunction syndrome and fatal outcome (27). While there is no doubt about the importance of monitoring the potential development of disseminated intravascular coagulation in sepsis, its confirmation often means decompensated coagulopathy, with significant reductions in platelet, fibrinogen and clotting factor levels (16), when therapy options have minimal effects, so efforts are made to identify and treat coagulopathies in sepsis before the development of this syndrome.

The mortality rate from sepsis increases when it is complicated by disseminated intravascular coagulation. Consequently, early detection and appropriate treatment of this severe coagulation disorder will be useful in the treatment of sepsis. The criteria for acute disseminated intravascular coagulopathy are not designed for its detection at an early stage. The criteria and scoring system for sepsis-induced coagulopathy were developed and introduced in 2017 to detect disseminated intravascular coagulation at an early stage and were subsequently adopted by the International Society of Thrombosis and Haemostasis in 2019. The aim of detecting sepsis-induced coagulopathy was not to overlook patients at high risk of developing acute disseminated intravascular coagulation at a later stage of sepsis development. Calculating the score of sepsis-induced coagulopathy is simple and convenient for use in clinical settings, and this new diagnostic criterion aims at timely recognition and better treatment of coagulopathy associated with sepsis (28).

The importance of early detection of fibrinolysis disorders in sepsis

One of the postulates related to sepsis, is that prompt diagnosis and quick care are necessary, so it would be of great importance to diagnose various forms of coagulopathies in sepsis at the very beginning of their occurrence, for the sake of an adequate therapeutic approach. However, current guides on sepsis, recognize mainly acute disseminated intravascular coagulation and suggest therapy with blood components in the case of vitally threatening deficits of coagulation factors, but without reference to the possibility of deficiency prevention and early recognition (29).

The modern point of view related to the timely detection of coagulopathies in sepsis can be seen through the comparison of the parameters of the score of sepsis-induced coagulopathy in relation to the score of disseminated intravascular coagulation. Namely, while the score of sepsis-induced coagulopathy (Table 3), scores the level of platelets in the range of $\geq 100 < 150$ x 109/L (16), the score of disseminated intravascular coagulation (Table 4), scores the level of platelets <100 x 109/L (30).

Given that early recognition is essential for improving the prognosis of manifested sepsis, it is of great importance to introduce routine additional tests that indicate abnormalities in the early phase of sepsis, which include pathological changes in coagulation and fibrinolysis. There is evidence that the clinical onset of sepsis is accompanied by impaired clot formation. Test-based fibrinolysis disorders have proven to be reliable biomarkers for the early identification of patients suffering from sepsis (9).

Evaluation of coagulation disorders in sepsis at an early stage allows clinicians to tailor treatment strategies based on individual patient profiles. This may include initiating anticoagulant therapy aimed at preventing further coagulation abnormalities and improving outcomes. Regular and timely monitoring of sepsis-induced coagulopathy helps clinicians monitor the progression of coagulopathy and assess the effectiveness of treatment over time. Likewise, the assessment of sepsis-induced coagulopathy helps stratify risk, allowing clinicians to identify patients who need more intensive monitoring or interventions to prevent adverse outcomes (28).

doi: 10.5937/mckg60-60288
COBISS . SR - ID 194792457
UDK. 616.94-074

Available laboratory markers of coagulopathy and fibrinolysis

Conventional Laboratory Coagulation Testing

Current conventional laboratory tests for coagulopathies that are also used in sepsis include: platelet level, Prothrombin time, International normalized ratio, Activated partial thromboplastin time, fibrinogen, D-dimer (1).

Viscoelastic Testing

Viscoelastic testing, including thromboelastography and thromboelastometry, provides a rapid and comprehensive picture of the dynamics of blood coagulation and hemostasis that can be examined and evaluated at the point of care for the patient (31).

Viscoelastic testing is based on the principles of measuring the change in the viscoelastic properties of whole blood during the formation of a clot. These tests analyze all phases of coagulation: initiation, amplification and propagation, thus reflecting the interactions of the cellular and plasma components of coagulation and the activity of the fibrinolytic system. Since they use whole blood, this makes it possible to assess the effect of cellular components of the blood on clot formation and strength (32). In relation to the added type of activator, the following trombelastometry tests are represented: Extrem, Intem, Fibtem, Aptem, Ecarin and Tissue plasminogen activator test, the characteristics and factors of which are given in Table 5 (33). The parameters of thrombolastometry tests are given in Table 6 (34).

A newer thrombolastometry test, with the addition of a recombinant tissue plasminogen activator, allows the detection of damage to clot breakdown, that is, damage to fibrinolysis - resistance to fibrinolysis. On the other hand, since in the early stages of sepsis, as we have already indicated, fibrinolysis is increased due to the conversion of plasminogen to plasmin by the enhanced action of the tissue activator plasminogen (1), in the detection of fibrinolysis damage, it would be important and early detection of increased fibrinolysis. In this sense, the routine introduction of the viscoelastic ecarin test in the monitoring of coagulation disorders in sepsis, which detects the occurrence of fibrinolysis in a larger number of patients nine minutes earlier, compared to other viscoelastic tests, could be of importance. Tissue plasminogen activator assays and ecarin assay can be considered complementary in practice in the detection of fibrinolysis disorders (33).

Euglobulin lysis time of the clot

The traditional, still available fibrinolysis test is the Euglobulin Clot Lysis Time. It is a method for quantifying fibrinolytic potential. The test measures the stability of the clot, i.e. fibrinolysis, without the action of plasma inhibitors – antifibrinolytic proteins (α2-antiplasmin, thrombin-activated fibrinolysis inhibitor, plasminogen activator inhibitor – 1). The euglobulin fraction of plasma contains: fibrinogen, plasminogen, tissue plasminogen activator. The time of euglobulin lysis is a good test for assessing the endogenous activity of the tissue plasminogen activator, determined by the balance of plasma concentrations between the tissue plasminogen activator and the plasminogen activator inhibitor – 1 (35).

Plasma fibrinolysis factors and natural coagulation inhibitors

Available tests of plasma fibrinolysis invoices and coagulation inhibitors in routine work are:

- plasminogen: circulating plasma fibrinolysis factor,
- plasmin inhibitor: fibrinolysis inhibitor,
- AT III, protein C, protein S: natural inhibitors of coagulation (36).
- FXIII: a factor that contributes to the stabilization of fibrin (37), and which also reduces fibrinolysis by cross-reaction with alpha-2 antiplasmin (18).

DISCUSSION AND CONCLUSION

Sepsis is a life-threatening condition caused by infection and is a significant global health problem. Recent epidemiological studies have shown that mortality rates from sepsis have decreased, but that the incidence continues to increase (7). Sepsis remains the leading cause of death in critically ill patients worldwide (6).

Some of the most prevalent disorders in sepsis are hemostatic disorders. Sepsis-induced coagulopathy is a common complication, occurring in 24% of patients with sepsis and 66% of patients with septic shock, and is often associated with poor clinical outcomes and high mortality (16). The fibrinolytic system is crucial in regulating intravascular deposition and clearance of fibrin, maintaining hemostasis, and avoiding thrombosis (17). Damage to the fibrinolytic system is increasingly considered a key factor in sepsis-induced coagulopathy. Impaired fibrinolysis in sepsis can contribute to undesirable outcomes such as microvascular thrombosis, organ dysfunction, and increased mortality (22).

Given that prompt diagnosis and quick care in sepsis are necessary, it would be of great importance to diagnose various forms of coagulopathies in sepsis at the very beginning of their occurrence, for the sake of an adequate therapeutic approach. In this regard, routine diagnostic tests are essential (29).

doi: 10.5937/mckg60-60288
COBISS . SR - ID 194792457
UDK. 616.94-074

When it comes to conventional hemostasis tests, they are a valuable way to measure coagulation capacities. However, they rely on individual tests of the coagulation cascade, and it is now known that hemostasis is much more interconnected and complex than previously thought (38).

These tests fail to fully define sepsis-induced coagulopathy. Abnormal values of standard coagulation tests are observed only late in the course of sepsis (in the stage of disseminated intravascular coagulation). In addition, conventional hemostasis screening tests provide data only on part of the hemostatic mechanism, as it is based on the plasma components of the coagulation system, while not evaluating the key contribution of cellular components. Furthermore, standard coagulation tests primarily evaluate the activity of procoagulant factors, without taking into account the concomitant activation of the anticoagulant mechanism (1).

Septic coagulopathy is a complex and dynamic entity of the disease, ranging from an initial hypercoagulability to a hypocoagulable state. However, the specific temporal kinetics of septic coagulopathy are characterized by high individual variability and the estimation of initial hypercoagulation using standard coagulation measurements is not feasible. So far it is not possible to reliably predict the critical turning point from hypercoagulation to hypocoagulation in an individual patient in the daily clinical routine (9).

In sepsis, the timely detection of fibrinolysis disorders would be significant. However, we currently have few options for evaluating fibrinolysis in routine diagnostics. Plasma concentrations of pro- and antifibrinolytic proteins do not provide dynamic information on fibrinolytic capacity. Plasma-based clot formation and lysis tests are available for research use, but due to a lack of automation and standardization, these tests are currently not suitable for routine clinical use (22).

In contrast, viscoelastic testing provides a rapid and comprehensive picture of the dynamics of blood coagulation and hemostasis that can be examined and evaluated at the point of care (32, 39). Compared to conventional coagulation tests, viscoelastic coagulation tests allow the detection of various forms of impaired coagulation balance: hypo- and hypercoagulation states, hyperfibrinolysis and hypofibrinolysis, and are superior in detecting the early stage of sepsis-induced coagulopathy. Initial hypercoagulation due to interruption of fibrinolysis, as indicated by an increased lysis index in viscoelastic tests, in the presence of other viscoelastic signs of hypercoagulation, can be used to identify hypercoagulant septic patients who are likely to benefit from anticoagulant therapy (9, 31, 32, 39).

Viscoelastic tests are suitable for acute conditions because they have a short operating time and are semi-automated. Moreover, because viscoelastic tests use whole blood, they allow for a global assessment of fibrinolysis that considers the influence of cellular components on the fibrinolytic process. Previous viscoelastometry tests have been based on the assessment of pathological hyperfibrinolysis and designed to diagnose possible causes of bleeding in patients, but newer viscoelastic tests have shown sensitivity to hypofibrinolysis. With the addition of tissue plasminogen activator, a test was obtained that can assess the level of resistance to fibrinolysis, i.e. the level of damage to the mechanism of physiological fibrinolysis, which is considered one of the first signs of sepsis-induced coagulopathy, which, due to impaired microcirculation, can cause organ damage in sepsis (22). A reduced clot lysis index after 30 minutes from the onset of clot formation, indicates the first stage of hypofibrinolysis (31). This index and other parameters of viscoelastic assays have been shown to be superior in detecting early-stage sepsis-induced coagulopathy compared to conventional hemostasis tests (32, 39).

A group of authors present the results of viscoelastic testing in patients with septic shock, who had normal prothrombin time and activated partial thromboplastin time, and early disorders in viscoelastic testing, and pointed out their importance in the timely initiation of anticoagulant therapy, in order to preserve homeostasis and avoid the adverse effects of coagulopathy (40).

However, the main disadvantage of viscoelastic testing is the higher cost of reagents and labor, and their routine use in coagulation tests is unwarranted in stable patients in an outpatient setting (38). The weakness of viscoelastic coagulation tests is that they are performed in vitro conditions, with or without an additional activator. Likewise, these tests cannot determine the contribution of the endothelium to coagulation (32). It is also unclear whether viscoelastic tests are sensitive enough to detect early changes in coagulation characteristic of sepsis-induced coagulopathy. This highlights the need for additional clinical research to determine viscoelastic reference ranges for sepsis-induced coagulopathy (16).

When interpreting fibrinolysis disorders with tests such as viscoelastic tissue plasminogen activator, we must not ignore the effect of elevated fibrinogen levels, which as an inflammatory marker, is often elevated in sepsis (23). The amplitude of the fibrin clot formed in the viscoelastic fibtem test is closely correlated with plasma fibrinogen levels (41). However, correlation analyses between the amplitude ten minutes after initiation of fibrin clot formation in the fibtem assay and the lysis time of the tissue plasminogen activator assay in patients with a lysis time of ≤ 300 seconds and those with a lysis time > 300 seconds, showed that in patients with a lysis time of > 300 seconds, the degree of resistance to fibrinolysis was not due to the formation of larger fibrin clots, as observed in

doi: 10.5937/mckg60-60288
COBISS . SR - ID 194792457
UDK. 616.94-074

patients with a lysis time ≤ 300 seconds. These data suggest that fibrinogen is the leading factor determining the lysis time in the tissue plasminogen activator assay when fibrinolysis is occurring normally; however, this bond is lost when resistance to fibrinolysis occurs, most likely due to a change in the balance of other factors, such as pro- and antifibrinolytic protein activity (23).

Also, attention should be paid to the complexity of the regulation of the fibrinolytic system, and that there are still many doubts. In terms of manifested resistance to fibrinolysis, in patients with sepsis in intensive care, often with numerous comorbidities and conditions, pay attention to fact that low fibrinolytic activity may also mean a temporary physiological state of fibrinolysis shutdown after previous systemic activation of the fibrinolytic system, i.e. a state of chronic hypofibrinolysis in obese, smokers, hypertensive patients and patients with previous vascular thrombotic episodes. There is also no doubt about the effect of endothelial dysfunction on the fibrinolytic process, and we do not currently have available means to routinely test the effect of endothelium on fibrinolysis (42).

Also, by reviewing the literature available to the authors so far, it can be determined that the results of the study showed a significant difference in fibrinolysis between patients with sepsis and healthy subjects, i.e. patients with sepsis compared to patients with septic shock (43). However, more research is needed to address this disorder in relation to the severity of organic dysfunction, i.e. in relation to the level of scoring sequential organ failure in sepsis, as well as in the early stage of disease manifestation. This could provide a greater benefit for the evaluation of this disorder in clinical practice and in the early stages of the disease and the subsequent application of timely adequate therapy (7).

The main advantage of viscoelastic testing is that the lysis index is a reliable biomarker of sepsis, more reliable in critically ill patients with sepsis compared to procalcitonin, interleukin 6 and C-reactive protein (32). However, the standardization and validation of these tests still need improvement and high-quality clinical trials remain needed to determine their exact place, benefit and cost effectiveness (44).

And the time of euglobulin lysis directly depends on the level of fibrinogen in the plasma. Therefore, with elevated fibrinogen levels, interpreting the results of euglobulin lysis time in terms of fibrinolysis disorders should be done with caution (45).

Given the complex and insufficiently researched regulation of fibrinolysis, all available testing modalities should be used in tests of impaired fibrinolysis in sepsis-induced coagulopathy, in order to reach the most reliable conclusions, both whole blood (16, 17, 22, 23, 34), as well as circulating plasma fibrinolysis factors, fibrinolysis inhibitors, and natural coagulation inhibitors (36), as well as FXIII, which contributes to the stabilization of fibrin (37), and also reduces fibrinolysis (18).

By reviewing the literature available to the authors, we can conclude that the research of fibrinolysis disorders within sepsis-induced coagulopathy is academically and clinically justified, that emphasis in future research should be placed on early detection of disorders for timely therapy, as well as in relation to the level of organic dysfunction in sepsis, and also to enable simplification of the interpretation of results and improvement of standardization of these tests in order to provide an individual therapeutic approach to the patient.

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